

# Mixed Connective Tissue Disorder and Castleman's Disease

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## Abstract

We present a 16 year old girl who presented with polyarthritits in association with Raynaud's phenomenon, malar rash, oral ulcers, photosensitivity and alopecia of 6 months duration. On evaluation, it emerged that she had a mixed connective tissue disorder with a mesangio-proliferative glomerulonephritis. Her Chest radiograph revealed a well defined left mid and lower zone opacity with evidence of a hilar mass on CT Thorax. Histopathological examination following CT guided biopsy of the mass revealed a hyaline vascular type of Castleman's disease. Mixed Connective Tissue Disorder with Castleman's Disease is a rare association; the patient presenting with varied and interesting manifestations. It is important to understand this association in view of management. The exact etio-pathogenesis of the autoimmune manifestations in patients with Castleman's disease is not clear. Treatment with immunosuppression can suppress both immune manifestations and result in tumour regression as well.

## Introduction

Castleman's disease, first described in 1956, is also known as angiofollicular mediastinal lymph node hyperplasia, angiomatous lymph node hyperplasia, giant benign lymphoma or benign giant lymph node hyperplasia.<sup>1</sup> It is a rare, heterogeneous group of atypical lymphoproliferative disorders which occur due to lymphoid follicle hyperplasia and marked capillary proliferation with endothelial hyperplasia.<sup>2</sup> It is a reactive, rather than a neoplastic, disorder caused by an antigenic stimulus or faulty immunoregulation. The varieties of Castleman's disease are the hyaline-vascular type (85-90%) and the plasmacytoid type.<sup>1</sup> Most of these tumours occur in the mediastinum or abdomen, though they may present with lymph node masses in the periphery (10-15%).<sup>1,2</sup>

Castleman's disease most often presents with asymptomatic lymph node masses or, especially in the multicentric variety, with systemic symptoms like fever, malaise, weight loss, anorexia and organomegaly. There are reports of autoimmune manifestations

such as haemolytic anemia and thrombocytopenia in Castleman's disease. There are also reported associations of Castleman's disease with Systemic Lupus Erythematosus (SLE), Rheumatoid arthritis, Myasthenia Gravis and Sjogren's syndrome.<sup>3</sup> We present a case of a young girl who had clinical manifestations of a mixed connective tissue disorder (MCTD) along with a mediastinal mass, a biopsy of which was suggestive of a hyaline-vascular variety of Castleman's disease.

## Case History

A 16 year old girl from Mizoram, India presented with polyarthritits of the small and large joints along with Raynaud's phenomenon, malar rash, oral ulcers, photosensitivity and alopecia of 6 months duration. Two months into the illness, she developed progressively worsening pedal oedema and a rash involving the dorsum of the fingers and toes associated with intermittent low grade fever. She also complained of a mild non-productive cough with minimal breathlessness for 3 months duration. There was no history of tightening of skin, dysphagia, proximal muscle weakness, psychosis, or seizures. There was no history of haemoptysis, loss of weight or appetite.

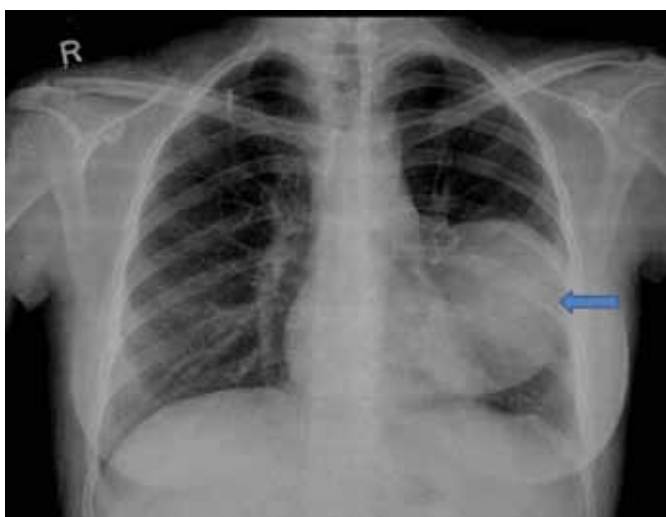


Fig. 1 : X-Ray Chest showing a well defined homogenous opacity in the left middle and lower lung zones



Fig. 3 : X-Ray Chest showing marked resolution of the opacity

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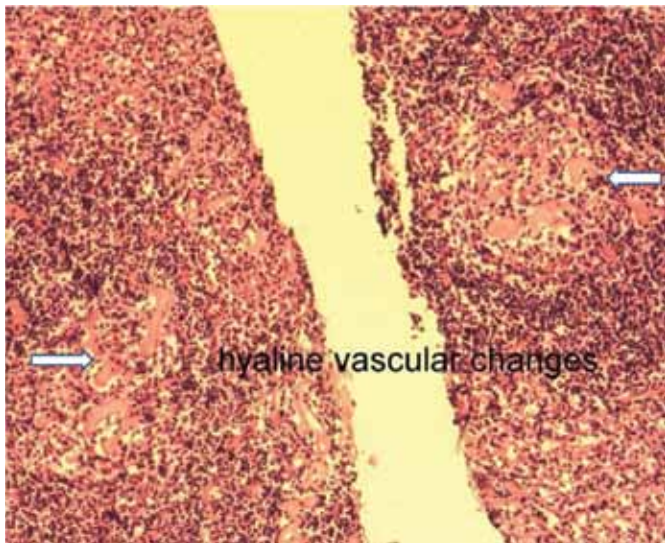


Fig. 2 : 100X Hyaline vascular change of Castleman's disease

Physical examination revealed a malar rash with telangiectatic lesions over the palms and soles and sausage-shaped swollen digits. She had alopecia and multiple palatal oral ulcers. Systemic examination was unremarkable except for anasarca and free fluid in the abdomen with no features of cardiac failure. Laboratory investigations revealed a mild anaemia (Haemoglobin 9.6g%, mean corpuscular volume (MCV) 70fL, Reticulocyte count 1.13%, direct Coombs test (DCT 1+). She was found to have a speckled-positive antinuclear antibody (ANA) with double stranded DNA (DsDNA) within normal limits, a positive rheumatoid factor (RF) and Anti Ribonucleoprotein (Anti U<sub>1</sub>RNP) of 136 U/ml (normal <20 U/ml). Complements were low (<60%). She had nephrotic range proteinuria (7.9 gm/760ml urine collected in 24 hrs); subsequent renal biopsy revealed mesangio-proliferative glomerulonephritis. A well-defined left mid and lower zone opacity was noted on chest radiograph (Figure 1) with an 8 x 7cm peripherally enhancing soft tissue density mass in the left hilum extending into the adjacent lung on CT Thorax. Histopathological examination following CT guided biopsy of the lung mass revealed a hyaline-vascular type of Castleman's disease (Figure 2).

A final diagnosis of MCTD with Castleman's disease was made. She was initiated on steroids (T. Prednisolone 1mg/kg), Azathioprine (1mg/kg) and Hydroxychloroquine (200mg once daily). Surgical removal of the mass was deferred as she was considered at high risk for surgery in view of severe hypoalbuminemia due to nephrotic syndrome. Follow up after 3 months revealed significant resolution of clinical features of the mixed connective tissue disorder. Repeat imaging of the lung mass revealed marked reduction in its size (Figure 3). A plan was made to surgically remove the mass at a later date if there is difficulty in controlling the autoimmune signs and symptoms, or if the mass significantly increases in size despite therapy.

## Discussion

The exact relationship between Castleman's disease and autoimmune diseases such as SLE is unclear and it is ambiguous whether the Castleman's tumour results in autoimmune manifestations or vice versa. Diseases such as SLE may have

lymphadenopathy whose histopathology is compatible with a diagnosis of Castleman's disease.<sup>4</sup> Certain authors suggest that the two disorders co-exist in the same patient and others suggest that Castleman's disease mimics autoimmune syndromes. Hence, in a given patient a clear distinction between the two entities may be difficult.

Though the exact cause of Castleman's Disease is not known, it appears to be polyclonal in origin in majority of the cases. Autoimmune dysregulation may be a reason for the apparent association of Castleman's disease with connective tissue disorders such as Systemic Lupus Erythematosus<sup>5,6</sup> and an overlap spectrum such as mixed connective tissue disease.<sup>7</sup> B cell disorders such as multiple myeloma, Waldenstrom's macroglobulinemia and Castleman's disease can occasionally manifest autoimmune traits during their course. It has thus been hypothesized that chronic stimulation of B cell clones, especially CD 5+, by B lymphocyte stimulator (BLyS) could result in the manifestation of autoimmune disease as well as lymphoproliferative disorders including Castleman's disease.<sup>3</sup> Some researchers speculate that increased production of interleukin-6 (IL-6) may be integral in the development of Castleman's Disease.<sup>6</sup> Other associations with Castleman's disease are human herpes virus 8 [HHV 8], the Epstein Barr virus, the human immunodeficiency virus,<sup>8</sup> pemphigus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) and Hodgkin's lymphoma.<sup>1</sup>

Various treatment modalities are available including surgical resection in unifocal varieties of Castleman's disease, steroids, and in certain cases, chemotherapy or radiotherapy.<sup>9</sup> Ganciclovir has also been advocated as therapy since it targets HHV 8. In this setting of connective tissue disorder with Castleman's disease, the use of steroids and other immunosuppressants to target the underlying collagen vascular disease would be the ideal initial therapy with close follow-up to assess response to therapy. There are case reports suggesting that the presence of Castleman's disease along with an autoimmune collagen vascular disease results in difficulty in achieving remission of the autoimmune manifestations with immunosuppressants that are conventionally used, such as steroids, Azathioprine and cyclophosphamide. Whether steroids and immunosuppressants alone are adequate in treatment of such conditions, or removal of the mass is also needed, has not been well documented or studied. Monoclonal antibodies against CD20 like Rituximab<sup>10</sup> and IL 6 have been described as effective agents in treating both conditions individually. This case highlights the association of collagen vascular disease and Castleman's disease, both known to result from immune dysregulation, and the possibility of treatment with immunosuppressants to achieve remission of both diseases.

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